

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA68; The clinical effectiveness and cost effectiveness of photodynamic therapy for age-related macular degeneration, TA155; Pegaptanib and ranibizumab for the treatment of age-related macular degeneration, and TA294; Aflibercept solution for injection for treating wet age related macular degeneration

This guidance was issued in: TA68 – September 2003; TA155 – August 2008; TA294 – July 2013.

The review date for this guidance (TA68/TA155/TA294) is February 2014.

1. Recommendation

TA 68, TA155 and TA294 should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

TA68: To establish the clinical and cost-effectiveness of photodynamic therapies for age-related macular degeneration (AMD) relative to current practice and in relation to their licensed indications and in order to produce guidance to the NHS in England and Wales.

TA155: "To appraise the clinical and cost effectiveness of anecortave acetate, ranibizumab and pegaptanib in their licensed indications for age-related macular degeneration". After the referral of the remit to NICE, the application for marketing authorisation for anecortave acetate was withdrawn by the manufacturer.

TA294: To appraise the clinical and cost effectiveness of aflibercept solution for injection, within its licensed indication, for the first line treatment of wet age-related macular degeneration.

3. Current guidance

TA68

- 1.1 Photodynamic therapy (PDT) is recommended for the treatment of wet age-related macular degeneration for individuals who have a confirmed diagnosis of classic with no occult subfoveal choroidal neovascularisation (CNV) (that is, whose lesions are composed of classic CNV with no evidence of an occult component) and best-corrected visual acuity 6/60 or better. PDT should be carried out only by retinal specialists with expertise in the use of this technology.

- 1.2 PDT is not recommended for the treatment of people with predominantly classic subfoveal CNV (that is, 50% or more of the entire area of the lesion is classic CNV but some occult CNV is present) associated with wet age-related macular degeneration, except as part of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including data on optimum treatment regimens, long-term outcomes, quality of life and costs.
- 1.3 The use of PDT in occult CNV associated with wet age-related macular degeneration was not considered because the photosensitising agent (verteporfin) was not licensed for this indication when this appraisal began. No recommendation is made with regard to the use of this technology in people with this form of the condition.
- 1.4 Patients currently receiving treatment with PDT could experience loss of well-being if their treatment is discontinued at a time they did not anticipate. Because of this, all NHS patients who have begun a course of treatment with PDT at the date of publication of this guidance should have the option of continuing to receive treatment until their clinical condition indicates that it is appropriate to stop.

TA155:

- 1.1 Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:
 - all of the following circumstances apply in the eye to be treated:
 - the best-corrected visual acuity is between 6/12 and 6/96
 - there is no permanent structural damage to the central fovea
 - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
 - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)and
 - the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).
- 1.3 Pegaptanib is not recommended for the treatment of wet age-related macular degeneration.
- 1.4 People who are currently receiving pegaptanib for any lesion type should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

TA294

- 1.1 Aflibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if:

- it is used in accordance with the recommendations for ranibizumab in NICE technology appraisal guidance 155 (re-issued in May 2012) and
- the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.

1.2 People currently receiving aflibercept solution for injection whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

4. Rationale¹

TA68

There is evidence to suggest that PDT is less cost effective than was originally estimated in the development of TA68. However, the use of PDT has declined markedly since the introduction of anti-VEGF agents (see Appendix 3 – Implementation submission) and this suggests that TA68 has already been superseded by subsequent guidance and that it might not be an efficient use of resources to update it at present. PDT has been studied in combination with ranibizumab and these studies have not found the addition of PDT to ranibizumab to be beneficial. There are further ongoing studies of PDT in combination with anti-VEGF agents and these might provide a reason to review TA68 later in the context of an MTA if it is decided that TA155 and TA294 should be reviewed.

TA155

There is no new evidence to suggest that the guidance in relation to pegaptanib requires update at present, nor are there any relevant ongoing studies.

The only new evidence that could suggest that a review of TA155 could be appropriate is that of published and ongoing studies comparing ranibizumab with bevacizumab.

NICE could only add value by carrying out such an update if it could appraise bevacizumab as an intervention, and formulate recommendations on its use in the NHS. Bevacizumab does not have a marketing authorisation for the treatment of wet age-related macular degeneration and is not formulated for use in the eye. As an unlicensed product, it can only be appraised if NICE receives a specific referral to do so from Ministers. It is not anticipated that such a referral will be made.

Furthermore, we are reminded of the conclusions of a workshop held in 2010 by NICE to explore the feasibility of appraising the use of bevacizumab to treat eye conditions in which ‘stakeholders agreed that an appraisal would need to be conditional on, or incorporate the assessment of, the safety and quality of intravitreal bevacizumab by a regulatory body or through the involvement of regulatory expertise’, and that ‘options for commissioning the relevant skills and expertise for

¹ A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

this purpose be explored', plus that 'arrangements for safety monitoring / pharmacovigilance will need to be explored'.

Finally, we note that the patient access scheme was revised twice; in 2012, leading to reissuing of the guidance, and again in 2013 as a result of a change in the discount offered.

On balance, we consider it reasonable to propose **not** to review TA155, and therefore place it on the static list.

TA294

There are 2 ongoing trials comparing ranibizumab with aflibercept. These will add further strength to the evidence base used to develop TA294 but are unlikely to overturn the guidance. There are ongoing studies of aflibercept following unsuccessful treatment with other anti-VEGF treatments but these are outside the current remit, which is limited to first-line treatment.

5. Implications for other guidance producing programmes

The Department of Health have commissioned a clinical guideline on the diagnosis and management of macular degeneration. CCP intends to formally commission the guideline to a developer once the outcome of this review proposal is agreed.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from June, 2011 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Changes to the marketing authorisations

Prior to the publication of TA68, the marketing authorisation for verteporfin (the photo sensitive agent used in PDT) included CNV of the occult form. However, the clinical and cost effectiveness of PDT in occult CNV was not considered in TA68 because of a lack of evidence. The indication of occult CNV was removed from the SPC in 2007 because of 'conflicting evidence'; therefore the current review will not be considering evidence in occult CNV.

Changes have been made to the dosing schedule in the SPC for ranibizumab since the publication of TA155. When TA155 was published, the dosing schedule was 3 monthly injections with retreatment if 5 or more letters were lost. This was changed in July 2011 to monthly treatment that is continued until visual acuity is stable for 3 consecutive months. It is unclear whether this affects the cost effectiveness of ranibizumab.

The marketing authorisation for pegaptanib has not changed since the publication of TA155. The SPC for pegaptanib was changed in 2007 to recommend that pegaptanib be stopped after 2 injections where there is a lack of benefit at 12 weeks. A stopping rule was not specified prior to the publication of TA155, however, in the health economic model, treatment was assumed to be stopped if visual acuity dropped below 6/96 or by 6 or more lines from baseline (scenario A), or below 6/60 (scenario B) at 1 year. This change in stopping rule may affect the cost effectiveness of pegaptanib.

The marketing authorisation for aflibercept in regards to macular degeneration has not changed since the publication of TA294.

Price and patient access schemes

The list price has not changed for verteporfin, ranibizumab, pegaptanib or aflibercept since their respective guidance were published. The vial size of ranibizumab was changed in 2008 from 0.3mL to 0.23mL, but the cost per single-use vial remains the same.

Verteporfin and pegaptanib do not have a patient access scheme (PAS).

A PAS was available for ranibizumab during the development of TA155 (drug cost of any subsequent injections after the first 14 injections is paid by the manufacturer), but it was not included in the economic model. The PAS was revised in 2012 (change to a simple, confidential, discount) and TA155 was reissued to incorporate this change. The PAS for ranibizumab was revised again in 2013 (change in the level of discount). The guidance has not been reissued to incorporate the 2013 change in the PAS. The change in the PAS is likely to make ranibizumab more cost effective, and therefore is unlikely to change the existing positive recommendation.

A PAS was available for aflibercept during the development of TA294 (a simple, confidential, discount) and was included in the cost effectiveness analysis. The PAS was revised in 2013 (change in the level of discount).

Comparators

There have not been changes to the available comparators since the publication of TA68, TA155 and TA294. However, there have been changes to the level of evidence available for bevacizumab (a comparator in both TA155 and TA294). See summary of new evidence for TA155 for further details.

Summary of new evidence

TA68 photodynamic therapy

The original guidance compared photodynamic therapy with a photosensitive agent (verteporfin PDT) with best supportive care for subfoveal CNV. TA68 recommended further research on the use of PDT for individuals with predominantly classic subfoveal CNV to determine the optimum treatment regimen and long-term benefit of PDT, and to add to the current evidence on quality of life. Two ongoing placebo controlled trials of verteporfin PDT were noted in the research recommendations in TA68, 1 in patients with minimally classic CNV using standard or reduced laser settings (VIM [Visudyne in minimally classic CNV]), and 1 in patients with occult CNV

(VIO [Visudyne in occult CNV]) These RCTs are now published and were identified during the review of TA68 in October 2010. However, the VIO refers to occult CNV and is outside of the marketing authorisation. The VIM study refers to minimally classic CNV however it does not address the lack of evidence for predominantly classic CNV mentioned in TA68.

One cohort study (verteporfin photodynamic therapy cohort study) highlighted in the review decision paper in 2010 as on-going, has now completed. The cohort study compared data from the TAP trial, which was included in TA68, with data from clinical practice. Data from clinical practice was collected between June 2004 and September 2007, and the results of the cohort study were published in February 2012 (Reeves, 2012). The study included 6647 eyes (in 6223 patients) with macular degeneration, of which 4043 eyes (in 4043 patients) had neovascular age-related macular degeneration. In the study, 80.4% of patients had classic CNV, and 16.8% of all patients had some evidence of occult CNV, however, it is not clearly reported how many patients had classic with no occult CNV, predominantly classic with occult CNV, minimally classic CNV, or occult only CNV. The authors report that verteporfin PDT was used much less frequently in routine clinical practice than in the TAP trial, but the change in best corrected visual acuity (BCVA) at year 1 in the cohort study was in line with the TAP trial. Adverse reactions (immediately following treatment) were reported in 1.4% of first visits, and adverse events (recorded at subsequent visit, covering the interval between visits) were reported in 1.9% of first visits, both of which were lower than those reported in the TAP trial. The cohort study estimated a cost per QALY of £170,000 over 2 years of verteporfin PDT treatment. Sensitivity analyses produced a cost per QALY of between £91,000 (if the costs of best supportive care were 10 times greater than assumed in the base case) and £288,000 (if treatment frequency was taken from the TAP trial rather than the cohort study). All of the ICER estimates reported in the cohort study were higher than the most plausible ICERs stated in TA68, which ranged from £26,000 per QALY at 2 years for people with classic with no occult CNV to £164,000 per QALY at 2 years for people with predominantly classic with any element of occult CNV.

The literature search identified a further 10 publications, in addition to the 3 studies highlighted above, relevant to this appraisal (Bressler, 2013; Chen, 2010; Cunningham, 2011; Dunavoelgyi, 2011; Giustolisi, 2011; Krebs, 2013; Larsen, 2012 [MONT BLANC]; Ozturk, 2012; Rouvas, 2012; and Sivaprasad, 2011).

None of the publications identified from the literature search compared PDT with or without verteporfin with laser photocoagulation therapy, sham or no treatment (comparators in TA68), ranibizumab, pegaptanib or aflibercept (PDT was a comparator in TA155 and TA294).

One of the 10 publications (Bressler 2013) describes results from 2 RCTs that compared ranibizumab with verteporfin PDT (MARINA and ANCHOR, the key trials in TA155). In the RCTs, patients treated with ranibizumab were more likely to report being able to drive and have a vision of at least 20/40 compared with patients receiving verteporfin PDT.

Six of the publications examined the efficacy of PDT with or without verteporfin as part of a sequence of treatment, including in combination with anti-VEGF drugs (Larsen, 2012 [MONT BLANC], Giustolisi, 2011; Krebs, 2013; Chen, 2010; Rouvas,

2012; and Cunningham, 2011). The 6 publications examined the efficacy of PDT with or without verteporfin in combination with ranibizumab, 1 of which provided a retrospective analyses of the ANCHOR, MARINA and PIER trial data (the 3 trials providing the evidence in TA155) (Cunningham 2011). Two of the studies (Larsen, 2012 [MONT BLANC] and Krebs, 2013) suggest that ranibizumab alone is more effective than ranibizumab with verteporfin PDT. The other 4 studies (Chen, 2010; Cunningham, 2011; Giustolisi, 2011; and Rouvas 2012) suggest that there is no difference in the efficacy of verteporfin PDT in combination with ranibizumab compared with ranibizumab alone.

The remaining publications examined the efficacy of PDT in combination with triamcinolone (Rouvas, 2012), reduced fluence PDT (a reduced light dose of 25 J/cm² at 600mW/cm² compared with a standard light dose is 50 J/cm² at 600mW/cm²) (Dunavoelgyi, 2011), PDT in combination with pegaptanib (Ozturk, 2012) and a non-comparative pilot study examined verteporfin PDT, ranibizumab, dexamethasone and oral minocycline in combination (Sivaprasad, 2011). The studies suggest that PDT with triamcinolone is more effective than verteporfin PDT with ranibizumab, but that there is no difference in reduced fluence PDT compared with standard PDT, PDT in combination with pegaptanib compared with pegaptanib alone, and verteporfin PDT in combination with ranibizumab, dexamethasone and oral minocycline compared with PDT in combination with ranibizumab.

There is 1 ongoing trial comparing PDT with aflibercept (NCT01482910) and 1 ongoing trial comparing ranibizumab with ranibizumab in combination with verteporfin PDT (NCT01846273 [EVEREST II]). The results from these trials are due to report in July 2014 and April 2016 respectively.

There is new evidence to suggest that PDT is less cost effective than was originally estimated in the development of TA68 and there are ongoing studies examining the efficacy of PDT in combination with anti-VEGF agents, both of which suggest that a future review of TA68 might be appropriate.

TA155: ranibizumab and pegaptanib

Ranibizumab

The original guidance compared ranibizumab and pegaptanib with PDT for the non occult form of subfoveal wet AMD (classic no occult lesions or predominantly classic lesions) and best supportive care. Ranibizumab and pegaptanib were not compared with each other as they were not listed as comparisons in the scope because of insufficiencies in the evidence. The evidence for TA155 was based on 4 RCTs that compared ranibizumab with sham plus PDT (ANCHOR), ranibizumab with sham alone (MARINA and PIER), and ranibizumab plus PDT with sham plus PDT (FOCUS).

Bevacizumab was not included in the final scope for TA155 but the research recommendations included research into the cost-effectiveness of ranibizumab versus bevacizumab, evidence of long term outcomes with anti-VEGFs and evidence on optimal frequency and duration of treatments. Two RCTs (IVAN and CATT) were highlighted in TA294 as providing recently published evidence on the clinical efficacy and safety of bevacizumab compared with ranibizumab in people with wet aged related macular degeneration.

The literature search for TA155 identified 20 publications for ranibizumab, in addition to those identified for verteporfin PDT in TA68 (Biswas, 2011; Bressler, 2011; Bressler, 2013; Chakravarthy, 2012 [IVAN]; Chakravarthy, 2013 [IVAN]; Carneiro, 2012; Cunningham, 2011; Do, 2013 [CATT]; Holz, 2010; Jaffe, 2013; Kodjikian, 2013 [GEFAL]; Krebs, 2013; Li, 2013; Martin, 2011; Martin, 2012; Rakic, 2013 [HELIOS]; Rofagha, 2013 [SEVEN-UP]; Subramanian, 2010; Wolf, 2011; and Wykoff, 2013 [SAVE]).

Eleven publications identified from the literature search examined the efficacy of ranibizumab compared with bevacizumab. These are: 7 publications from 6 RCTs (Chakravarthy, 2012 [IVAN]; Chakravarthy, 2013 [IVAN]; Krebs, 2013; Kodjikian, 2013 [GEFAL]; Martin, 2011; Martin 2012; and Subramanian, 2010), a prospective cohort study within an RCT (Jaffe, 2013), a prospective comparative case series (Biswas, 2011), a prospective comparative study (Li 2013), a retrospective comparative study (Carneiro, 2012) and a retrospective review of the data from the CATT RCT (Do, 2013). The year 1 results of IVAN (Chakravarthy, 2012) were inconclusive, but the outcomes were consistent with the drugs having similar efficacy and safety. The year 2 results of IVAN (Chakravarthy, 2013) showed that bevacizumab was neither non-inferior nor inferior to ranibizumab (defined using a pre-specified non-inferiority limit of 35 letters), with no difference between the drugs in arterial thrombotic events, hospital admissions or mortality. The CATT trial (Do, 2013) showed that the drugs were equally effective at year 1. The other publications reported that the drugs had similar efficacy. One publication (Martin, 2012) reported a significantly higher proportion of patients with 1 or more systemic serious adverse events in the bevacizumab group. Two other publications suggested similar safety profiles (Biswas, 2011 and Kodjikian, 2013 [GEFAL]), and other publications advised that the rates of serious adverse events needed further study.

One publication modelled the clinical effectiveness of ranibizumab compared with no ranibizumab based on trial data from ANCHOR and MARINA (Bressler, 2011) and another modelled the clinical effectiveness of ranibizumab based on 12 month data from ANCHOR, MARINA and PIER (Holz, 2010). Bressler (2011) showed that ranibizumab should have a substantial effect on reducing the magnitude of legal blindness and visual impairment. Holz (2010) showed that a flexible individualised visual-acuity guided regimen could improve the cost-effectiveness of ranibizumab. The publication from Holz addresses the research recommendation in TA155 about the appropriate duration and optimal treatment regimen in terms of frequency of injections.

The remaining publications were non-comparative and included a prospective observational study of ranibizumab (Rakic 2013 [HELIOS]), a subgroup analysis of the ranibizumab groups in the MARINA and ANCHOR trials (Wolf 2011), a 7 year follow up of the ranibizumab groups in the ANCHOR, MARINA and HORIZON (an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration) trials (Rofagha, 2013 [SEVEN-UP]), and an RCT of ranibizumab every 4 weeks compared with every 6 weeks (Wykoff, 2013 [SAVE]). The studies suggested that ranibizumab is effective in improving visual acuity, and that there was no change in the frequency of adverse events with long term use. One publication (Wykoff, 2013 [SAVE]) reported that monthly treatment enabled visual gains to be sustained, but treatment every 6 weeks did not.

The updated literature search also identified 1 ongoing trial comparing ranibizumab with bevacizumab (NCT01127360 [LUCAS]), the results of which are expected in July 2014. This study is likely to address some of the uncertainty around the safety of bevacizumab compared with ranibizumab.

There is new evidence regarding the efficacy of ranibizumab compared with bevacizumab and more results are expected later this year from an ongoing study. The implementation submission (appendix 3) reports that there is continued interest in the NHS regarding the use of bevacizumab as its list price is lower than ranibizumab. However, reviewing the evidence for ranibizumab compared with bevacizumab would not allow a recommendation to be made regarding the use of bevacizumab. Bevacizumab does not have a marketing authorisation for the treatment of wet age-related macular degeneration and is not formulated for use in the eye. Bevacizumab therefore cannot be appraised by NICE unless NICE receives an exceptional direction to do so by the Department of Health. Unless NICE receives such direction, it would be unable to make a recommendation about bevacizumab if it were to be the most cost effective option. Reviewing the evidence for ranibizumab with bevacizumab as a comparator may prevent ranibizumab from being recommended, without providing an alternative treatment.

Pegaptanib

The literature search for TA155 identified 2 publications for pegaptanib, in addition to those identified for verteporfin PDT above (Feucht, 2008 and Nishimura, 2012). One was a retrospective non-comparative analysis of pegaptanib (Feucht, 2008) and the other was a retrospective comparison of pegaptanib and ranibizumab (Nishimura 2012). The results from these studies suggest that pegaptanib was well tolerated and showed good efficacy, and that there was no significant difference in mean BCVA between ranibizumab and pegaptanib at 1, 3, 6 or 12 months. No ongoing trials for pegaptanib were identified.

TA155 states that although pegaptanib was clinically effective, it was not cost effective. The price of pegaptanib has not changed and a patient access scheme has not been implemented. Therefore it is unlikely that a review of the guidance for pegaptanib would change the existing recommendations.

TA294: aflibercept

The final scope for this appraisal compared aflibercept with ranibizumab, bevacizumab and photodynamic therapy. At the time TA294 was undertaken, the Committee considered the manufacturer's decision to exclude bevacizumab and photodynamic therapy as comparators in its decision, despite being listed as comparators in the scope. In TA294 the Committee concluded that it was appropriate to exclude photodynamic therapy as a comparator because it would only be offered to patients with polypoidal choroidal vasculopathy, which is not related to AMD. This review does not consider aflibercept compared with PDT for this reason. In TA294, the Committee agreed to defer consideration of bevacizumab as a comparator until a review of the guidance. It also agreed that the review should coincide with a review of TA155 and should also include bevacizumab.

The literature search for TA294 identified 3 ongoing trials for aflibercept, all of which examine aflibercept as a 2nd or 3rd line treatment after other anti-VEGFs

(NCT02002377 [SHIFT-2], NCT01918878, NCT01896284 [MACBETH]). The results of these trials are expected in December 2017, September 2014, and March 2015 respectively. However these trials are outside the current remit of TA294, which is limited to first-line treatment. Two ongoing trials comparing ranibizumab with aflibercept were also identified (NCT01958918 [SALT] and NCT01988662 [UNRAVEL]). The results for these trials are expected in October 2015 and April 2015 respectively, and are unlikely to address uncertainty in the existing guidance.

No published or on-going trials were identified comparing aflibercept with bevacizumab.

The remit for TA294 specified the use of aflibercept as a first line treatment for wet age-related macular degeneration, although the marketing authorisation for aflibercept includes all lines of therapy. New evidence will be available in the future regarding the efficacy of aflibercept as a 2nd or 3rd line treatment, however, these are outside of the current remit, which is limited to first-line treatment.

8. Implementation

A submission from Implementation is included in Appendix 3.

Based on the implementation submission, it appears that NICE guidance on ranibizumab is being adhered to as ranibizumab prescribing has increased in line with NICE guidance. However, verteporfin use has decreased since October 2006 despite no change in the recommendations for verteporfin, and no new guidance being published in this disease area until August 2008.

The implementation consultants have provided qualitative input from the field team which suggests that the NHS are still interested in the clinical and cost effectiveness of ranibizumab compared with bevacizumab.

There was no information regarding the use of pegaptanib or aflibercept.

9. Equality issues

There were no equality issues raised in the original guidance.

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No
The guidance should be transferred to the ‘static guidance list’.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
 - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
 - There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
 - The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Macular oedema (central retinal vein occlusion) - aflibercept solution for injection
Technology appraisal TA305 Issued: February 2014

Epiretinal brachytherapy for wet age related macular degeneration. Interventional
Procedure Guidance. IPG415. Published: December 2011.

Macular translocation with 360° retinotomy for wet age related macular
degeneration. Interventional Procedure Guidance. IPG340. Published: May 2010.
Note: part replaces IPG48 (March 2004).

Limited macular translocation for wet age-related macular degeneration.
Interventional Procedure Guidance. IPG339. Published: May 2010. Note: part
replaces IPG48 (March 2004).

Implantation of miniature lens systems for advanced age-related macular
degeneration. Interventional Procedure Guidance. IPG272. Published: August 2008.

Transpupillary thermotherapy for age-related macular degeneration. Interventional
Procedure Guidance. IPG58. Published: June 2004.

Radiotherapy for age-related macular degeneration. Interventional Procedure
Guidance. IPG49. Published: March 2004.

Referred - QSs and CGs

Macular degeneration has been referred to NICE as a Clinical Guideline and Quality
Standard.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Fenretinide (Sirion Therapeutics)	In Phase III clinical trials
NT 501 (Neurotech Pharmaceuticals)	In Phase II clinical trials

Registered and unpublished trials

Trial name and registration number	Details
VEGF Trap-Eye: Investigation of Efficacy and Safety in Chinese Subjects With Wet AMD (Age-Related Macular Degeneration) (NCT01482910)	<p>This study will assess the efficacy and safety of intravitreally (IVT), i.e. directly into the eyeball administered VEGF Trap-Eye compared with photodynamic therapy (PDT) on visual function in Chinese subjects with age-related neovascular or "wet" age-related macular degeneration.</p> <p>Enrolment: 289</p> <p>Estimated study completion date: July 2014</p> <p>Status: Ongoing, but not recruiting participants</p>
Visual Outcome in Patients With Symptomatic Macular PCV Treated With Either Ranibizumab as Monotherapy or Combined With Verteporfin Photodynamic Therapy. (EVEREST II) (NCT01846273)	<p>Estimated Enrolment: 320</p> <p>Estimated Study Completion Date: April 2016</p> <p>Status: Currently recruiting participants.</p>
LUCAS (Lucentis Compared to Avastin Study) (NCT01127360)	<p>This protocol describes such a randomized multicenter study, performed in Norway, comparing ranibizumab and bevacizumab use for AMD. The goal of the study is to demonstrate if the two agents are equivalent regarding both efficacy and safety.</p> <p>Enrolment: 420</p> <p>Estimated Study Completion Date: July 2014</p> <p>Status: Ongoing, but not recruiting participants</p>

Trial name and registration number	Details
Treat and Extend Treatment With 0.5mg Ranibizumab vs Monthly Treatment With 0.5mg Ranibizumab (T-REX) (NCT01748292)	A treat and extend protocol starts with monthly injections until signs of activity have resolved with clinical and OCT confirmation. The interval between visits is then lengthened by 1 to 2 weeks as long as there are no signs of recurrent activity. Treatment is done at every visit but the time between visits is individualized based on a patient's response to treatment. When recurrent disease is detected, the treatment interval is reduced. The goal is to maintain an exudation-free macula with the fewest number of office visits, tests and injections Estimated Enrolment: 60 Estimated Study Completion Date: January 2015 Status: Currently recruiting participants
A Phase 3 Safety and Efficacy Study of Fovista™ (E10030) Intravitreal Administration in Combination With Lucentis® Compared to Lucentis® Monotherapy (NCT01940900)	Estimated Enrolment: 622 Estimated Primary Completion Date: July 2016 Status: Currently recruiting participants
Comparison of Treatment Regimens Using Ranibizumab: Intensive (Resolution of Intra- and Sub-retinal Fluid) vs Relaxed (Resolution of Primarily Intra-retinal Fluid) Treatment. (FLUID) (NCT01972789)	Estimated Enrolment: 330 Estimated Study Completion Date: November 2016 Status: Currently recruiting participants
Safety and Tolerability of Ranibizumab in Mono/Bilateral w-AMD Patients in Eyes With BCVA<2/10 and/or 2nd Affected Eye (TWEYES) (NCT01986907)	Estimated Enrolment: 5000 Estimated Study Completion Date: June 2016 Status: not yet open for participant recruitment
Impact of Home Monitoring to Decrease the Treatment Burden for Neovascular Age-related Macular Degeneration (AMD) (Liberty) (NCT01863199)	Estimated Enrolment: 60 Estimated Study Completion Date: May 2015 Status: not yet open for participant recruitment

Trial name and registration number	Details
Efficacy of Ranibizumab Prn Treatment Compared to Aflibercept Bimonthly Intravitreal Injections on Retinal Thickness Stability in Patients With Wet AMD (SALT) (NCT01958918)	Estimated Enrolment: 500 Estimated Study Completion Date: October 2015 Status: Currently recruiting participants
Randomized Study for Efficacy and Safety of Ranibizumab 0.5mg in Treat-extend and Monthly Regimens in Patients With nAMD (TREND) (NCT01948830)	Estimated Enrolment: 644 Estimated Study Completion Date: October 2015 Status: not yet open for participant recruitment
Intravitreal Aflibercept in Wet Age Related Macular Degeneration Patients With an Incomplete Response to Monthly Ranibizumab Injections (SHIFT-2) (NCT02002377)	Estimated Enrolment: 200 Estimated Study Completion Date: December 2017 Status: not yet open for participant recruitment
Aflibercept (EYLEA) as Secondary or Third Line Treatment for Neovascular Age-related Macular Degeneration. (NCT01918878)	Estimated Enrolment: 48 Estimated Study Completion Date: September 2014 Status: not yet open for participant recruitment
Study of PRN and Every 2months Intravitreal Aflibercept for Age Related Macular Degeneration (NCT01824225)	Estimated Enrolment: 100 Estimated Study Completion Date: March 2015 Status: on-going, but not recruiting participants
Study to Evaluate Efficacy of Aflibercept in Neovascular Age-related Macular Degeneration Patients Non Responders to Anti-Vascular Endothelial Growth Factor (NCT01896284)	Estimated Enrolment: 43 Estimated Study Completion Date: March 2015 Status: not yet open for participant recruitment
UNcovering the Difference Between Ranibizumab and Aflibercept, Focusing on Systemic Anti-VEGF Effects in Patients With neovascuLar AMD (UNRAVEL) (NCT01988662)	Estimated Enrolment: 204 Estimated Study Completion Date: April 2015 Status: not yet open for participant recruitment

Trial name and registration number	Details
Short-term Clinical Effects of Intravitreal Aflibercept Injection 2.0mg as a Predictor of Long-term Results (NCT01657669)	Estimated Enrolment: 20 Estimated Study Completion Date: February 2014 Status: Currently recruiting participants
Efficacy of Ranibizumab Prn Treatment Compared to Aflibercept Bimonthly Intravitreal Injections on Retinal Thickness Stability in Patients With Wet AMD (SALT) (NCT01958918)	Estimated Enrolment: 500 Estimated Study Completion Date: October 2015 Status: Currently recruiting participants

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Appendix 3 – Implementation submission

**Review of NICE technology appraisal guidance No. 68, 155 and 294;
Wet-aged macular degeneration - photodynamic therapy,
pegaptanib, ranibizumab and aflibercept**

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Contents

1. Routine healthcare activity data	24
2. Implementation studies from published literature	25
3. Qualitative input from the field team.....	26
Appendix A: Healthcare activity data definitions.....	28

1. Routine healthcare activity data

1.1. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of Verteporfin (used in photodynamic therapy) that has been prescribed and dispensed for use in hospitals in England between July 2000 and March 2012 (figure 1).

Figure 1 Cost and volume of Verteporfin prescribed and dispensed in hospitals in England

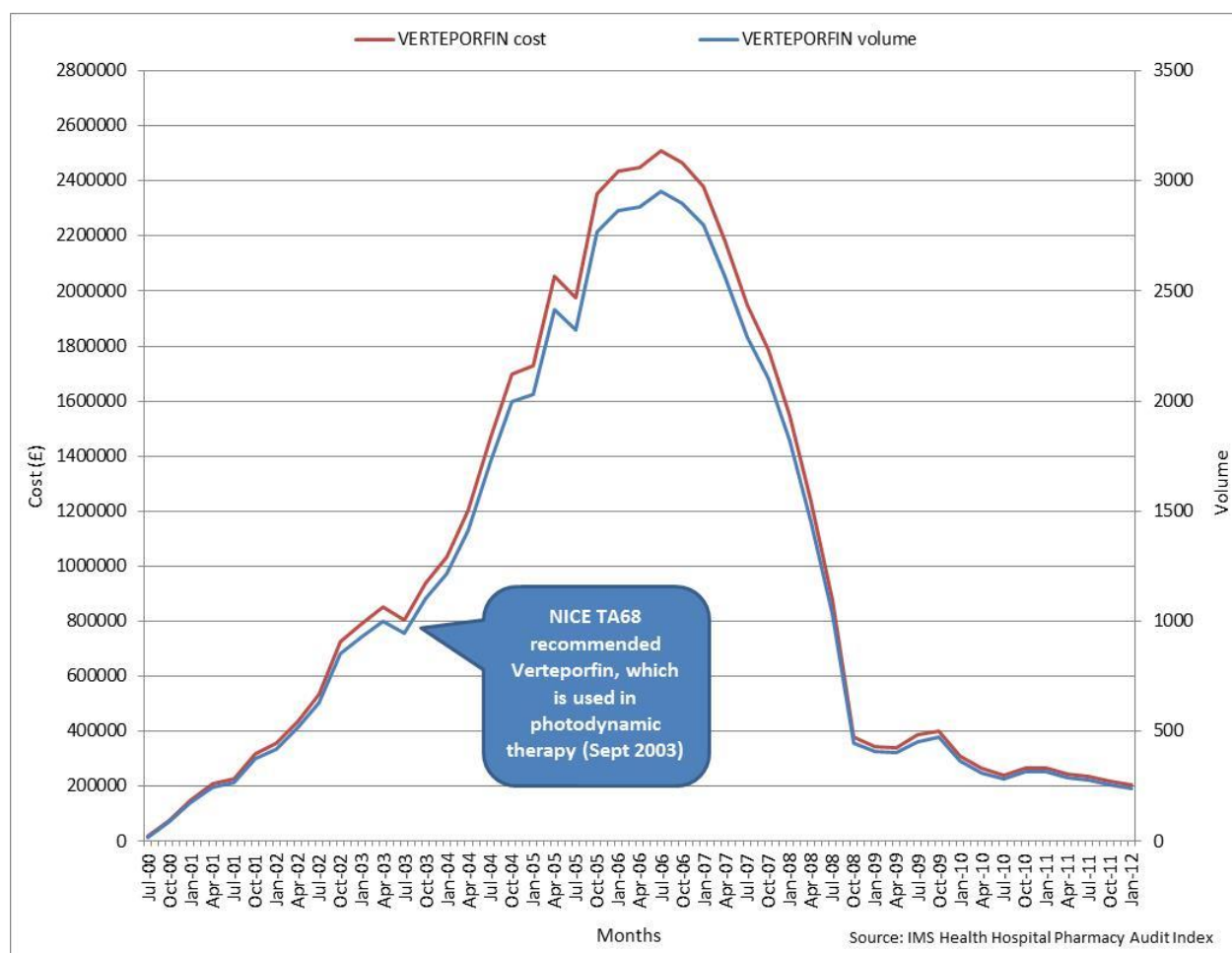
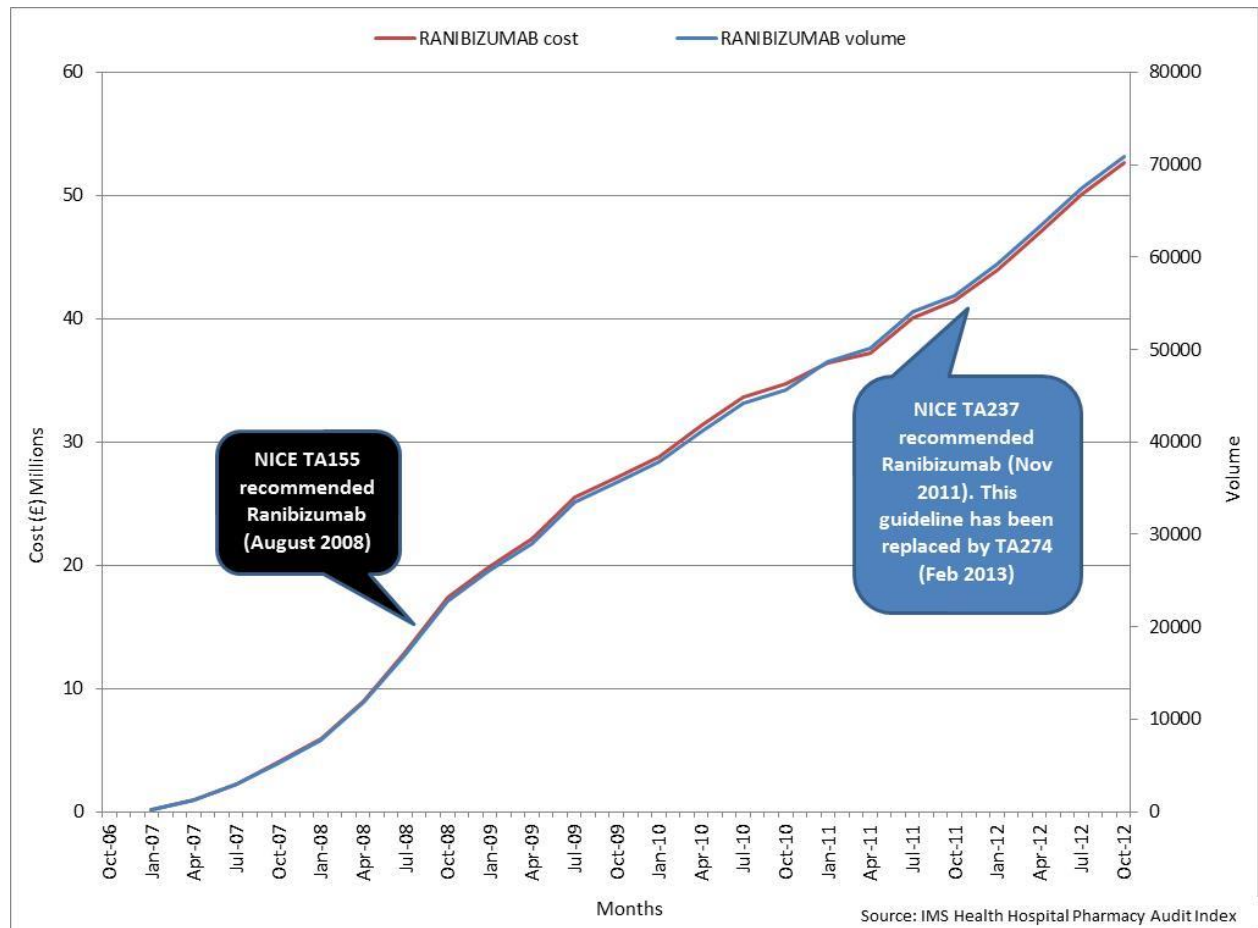


Figure 2 shows Hospital Pharmacy Audit Index data on the net ingredient cost and volume of Ranibizumab that has been prescribed and dispensed for use in hospitals in England between July 2000 and December 2012. These data need to be treated with caution as Ranibizumab has more than one indication.

Figure 2 Cost and volume of Ranibizumab prescribed and dispensed in hospitals in England



2. Implementation studies from published literature

Information is taken from the [uptake database](#) website.

2.1 The NHS Information Centre for Health and Social Care (2011) [Use of NICE-appraised medicines in the NHS in England-2009, Experimental Statistics](#)

This is the second report commissioned by the Metrics Working Group to look at the variation in use of positively appraised medicines in relation to the expected use as predicted by NICE. In all, 47 medicines in 18 groups, relating to 29 technology appraisals were considered. Out of the 12 groups where a comparison could be made (these are presented in Section 1 of the technology section results), observed use by the NHS in England was higher than the predicted use for eight and lower for three.

2.2 Richards, M (2010) [Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE](#)

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

2.3 Health and Social Care Information Centre (2012) [Use of NICE-appraised medicines in the NHS in England - 2010 and 2011, Experimental Statistics](#)

This is the 3rd report published by the HSCIC on behalf of the DH to look at the variation in use of positively appraised medicines in relation to the expected use as predicted by NICE. In all, 52 medicines in 25 groups, relating to 35 technology appraisals were considered. Out of the 12 groups where a comparison could be made, observed use by the NHS in England was higher than the predicted use for 6 and lower for 6. For one drug group use was lower on one measure, and higher on another.

2.4 Panneerdelvam, S. et al (2013) Ensuring that mandatory guidance is being correctly implemented: experience of using the NICE technology appraisal audit tool from TA 155 *Clinical Audit 2013:5 11:15*

This article describes the experience of Wolverhampton and Midland Counties Eye Infirmary in applying an audit tool for auditing the implementation of guidance on the use of ranibizumab and pegaptanib for the treatment of macular degeneration. Results from an initial audit of 30 patients seen between Jan-Apr 2011 showed 0-10% compliance with patient-centered care criteria. Results from a re-audit on 24 different patients seen between Jul-Sep 2011 shows compliance in these areas increased to 87.5%.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

- One person commented that they thought this was good guidance
- One person commented that the guidance had not caused the difficulties expected in terms of delivery and capacity
- Eleven people commented that the guidance had given them concerns over costs/funding
- Eleven people commented that they were keen to use Avastin over Lucentis due to costs
- One person commented that American studies had apparently suggested a small rise in complications using Avastin

- 14 people expressed an interest in NICE appraising Avastin for the treatment of AMD. One provider organisation concerned that their commissioners had instructed ophthalmologists to use Avastin instead of Lucentis going against guidance from the Royal College of Ophthalmologists
- 2 people expressed concern about difficulties in managing the patient access scheme associated with Lucentis

Appendix A: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.